REMARKS

In response to the Non-Compliant Amendment set forth in the Office Action of June 1, 2009, Applicants hereby submit an amendment compliant to each of the Examiner concerns. Specifically, claim identifiers have been amended to comply with the proper status identifier. Claims 5, 6, 17 and 18 are all "Withdrawn." Additionally, Applicants thank the Examiner for careful examination of the claims, especially claim 13. Claim 13 has been corrected to remove the parentheses around "GAD_{65}" in the last line of the claim.

Applicants' response to the remaining grounds for rejection have not changed and reference is made to the February 23, 2009, submission for the remarks. For convenience, the response has been copied below.

Status of the Claims

Claims 1-24 are pending in the instant application. Claims 5, 6, 17, and 18 have been withdrawn pursuant to 37 CFR 1.142(b) as being drawn to non-elected species. Applicants amend claims 1, 3, 4, 13, 15, 16, 22, and 23 and cancel claim 8 and 20. Support for such amendments can be found throughout the specification, and with respect to claims 1 and 13 in particular, in claims 8 and 20 respectively. No new matter is added. Applicants previously added claims 22 and 23 and now add new claim 24, which further recites the amelioration of symptoms of a (neurodegenerative) disorder. Support for these amendments can be found in the claims as originally filed and throughout the specification.

For the Examiner's convenience, Applicants resubmit the Declaration of Michael Kaplitt, which was originally submitted in the parent application App. Ser. No. 09/863,179 (now U.S. Patent No. 6,780,409) and was referenced in a previous response filed by Applicants in the present application, in support of their amendments and arguments. Both the Application and the cited references were of record in this application because they were of record in the parent case. Nevertheless, the Examiner did not consider the Declaration because the references cited therein were not "made of record." (Office Action p. 10.) Applicants now resubmit the November, 2003 Declaration of Michael Kaplitt, as well as all the references cited therein.

Applicants submit that the claims are allowable. Claims 5, 6, 17, and 18 are therefore subject to reinstatement because claims 1 and 13 are generic for the elected species.

The Invention

The claimed invention generally relates to methods for altering expression of a glutamic acid decarboxylase 65 (GAD_{65}) in a region of the brain. More specifically, the claims as they currently stand relate to methods of altering the level of GAD_{65} in the brain of a subject that requires such modification. This is accomplished by identifying a target site in the brain central that requires modification and delivering a vector that comprises a nucleic acid sequence encoding glutamic acid decarboxylase 65 (GAD_{65}) to a target site of the brain to alter expression of GAD_{65} in the region of the brain.

More specifically, the present application also discloses and claims a method of treating a disease by delivering a vector that comprises a nucleic acid sequence encoding glutamic acid decarboxylase 65 (GAD65) to target cells of the brain, to treat or reduce a neurodegenerative disease. Applicants have discovered that increased levels of GAD can ameliorate certain central nervous system (CNS) diseases, and that gene therapy can be used effectively to increase GAD in the central nervous system.

New claim 24 is drawn to a method of altering expression of glutamic acid decarboxylase 65 (GAD_{65}) in a brain of a subject having a neurodegenerative disorder that causes morphological and/or functional abnormality of a neural cell or population of neural cells. The method comprises identifying a target site in the brain that requires modification; stereotaxically delivering a vector comprising an adeno-associate virus and a nucleotide sequence encoding glutamic acid decarboxylase 65 (GAD_{65}) to the target site in the CNS; and expressing GAD_{65} in the target site.

In support of this application, Applicants hereby re-submit the November, 2003 Rule 132 Declaration of Dr. Michael Kaplitt (hereinafter "Kaplitt Decl.") regarding the scope of the invention, which was originally submitted in the parent application App. Ser. No. 09/863,179. Applicants note that the additional experiments referred to in the Kaplitt Decl. appear in full form

in U.S. Pub. No. 2005/0025746 (App. Ser. No. 10/802,497) (hereinafter "'746 Publication") (also attached for the Examiner's convenience), which is a continuation-in-part of the instant application.

Claim Objections

The Examiner objected to claims 1-4, 7-16, and 19-23 as being drawn to non-elected subject matter. Applicants submit that amended claims 1 and 13 are generic and allowable. Accordingly, this rejection should be withdrawn.

Double Patenting Rejection

The Examiner has maintained the rejection of claims 1-4, 7-16, and 19-23 on the grounds of non-statutory obviousness type double patenting as being unpatentable over claims 1-14 of U.S. Patent 6,780,409. Applicants submit the appropriate Terminal Disclaimer herewith.

Claim Rejection under 35 U.S.C. § 112 – Enablement

The Examiner has rejected claims 1-4, 7-16, and 19-23 under 35 U.S.C. § 112, first paragraph for lack of enablement. In particular, the Office Action asserts that:

> [t]he specification, while being enabling for a method of treating Parkinson's disease by administering to a region of the brain a vector comprising a nucleotide sequence a nucleotide sequence encoding glutamic acid decarboxylase (GAD), wherein the symptom of Parkinson's disease is ameliorated, *does not reasonably provide enablement for the use of any type of vector* for the treatment of any disease, *nor any target tissue other than the brain*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
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> (Emphasis added.)

As supporting this ground for rejection, the Office Action cites certain references suggesting that gene therapy is an unpredictable art, and as such, Applicants invention should be limited as stated above. Applicants disagree. Once Applicants' teachings with respect to GAD

expression are known, the design of particular vectors and the selection of various CNS sites is clearly within the capabilities of one skilled in the art.

It is well established that enablement is not precluded by the need for experimentation, even a large quantity of experimentation, if the specification, in combination with the knowledge available in the art, provides guidance regarding how to carry out the experimentation such that the experimentation is not "undue." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (citing *In re Angstadt*, 537 F.2d 489, 502-504, 190 USPQ 214, 218 (CCPA 1976)).

Furthermore,

> [t]he law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. *See Vivid Technologies, Inc. v. American Science and Engineering, Inc.* 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ("Patents are written by and for the skilled artisans"). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. Although an accommodation to the "common experience" of lay persons may be feasible, it is an unnecessary burden for inventors and has long been rejected as a requirement for patent disclosures. *See Atmel Corp.*, 198 F.3d at 1382, 53 USPQ2d at 1230 (Fed. Cir. 1999) ("The specification would be of enormous and unnecessary length if one had to literally reinvent and described the wheel."); *W.L. Gore & Assoc., Inv. v. Farlock, Inc.*, 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983) ("Patents are written to enable those skilled in the art to practice the invention, no the public.").
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> *S3 Inc. v. Nvidia Corp.*, 259 F.3d 1364, 1371 (Fed. Cir. 2001).

The Examiner is attempting to use this rejection to limit the scope of Applicants' claims to cover only the embodiment of the invention that is disclosed in the working examples. The specification of the present invention, however, provides adequate teaching and guidance to enable one of ordinary skill in the art to make and use the claimed methods of the present invention to treat neurodegenerative diseases using vectors carrying the GAD_{65} gene, and deliver these vectors to a region of the brain that requires modification with the GAD_{65} gene. The claims clearly recite

methods that are sufficiently enabled by the specification of the present invention. Accordingly, Applicants are entitled to claim coverage for all subject matter that one of ordinary skill in the art would gather from the teachings and guidance of Applicants' specification, as well as from the knowledge available in the art.

New claim 24 is drawn to a method of altering expression of glutamic acid decarboxylase 65 (GAD_{65}) in a brain of a subject having a neurodegenerative disorder which causes morphological and/or functional abnormality of a neural cell or population of neural cells. The method comprises identifying a target site in the brain that requires modification; stereotaxically delivering a vector comprising an adeno-associate virus and a nucleotide sequence encoding glutamic acid decarboxylase 65 (GAD_{65}) to the target site in the brain; and expressing GAD_{65} in the target site.

The working examples provided by the specification of the present invention are *merely illustrative* of the underlying inventive concept of Applicants' invention – they do *not* represent the sum total of Applicants' underlying inventive concept. Accordingly, the scope of Applicants' claimed methods should not be limited to only the use of the AAV vector or delivery to only the subthalmic nucleus. Applicants have provided adequate disclosure for other suitable vectors that can be readily substituted into the methods disclosed by the present specification to deliver the GAD_{65} gene to any region of the brain, not just the subthalmic nucleus. Applicants note, however, that dependent claims 4 and 16, as well as new claim 24, are limited to a vector comprising AAV.

Moreover, the working example demonstrates the proof-of-principle that GAD_{65} overexpression in a region of the brain associated with a neurodegenerative disease, such as Parkinson's disease, can help ameliorate the disease. The same methodology described in the application can readily be applied to other neurodegenerative diseases that require modification with GAD_{65}.

At the time the invention was filed (the priority application was filed in May, 2000), the knowledge available to the skilled artisan was well established for treating neurodegenerative diseases such as Parkinson's disease with gene therapy. Thus, gene therapy for neurodegenerative diseases such as Parkinson's disease was not an unpredictable art. In fact, a number of

representative articles are presented in the Kaplitt Decl. demonstrating that the skilled artisan recognized and used gene therapy as a means of treating neurodegenerative diseases. The skilled artisan has used a number of different vectors that deliver a particular desired gene, and can express the protein in the desired location in the central nervous system. Moreover, the skilled artisan has successfully delivered the vectors to different regions of the brain associated with a neurodegenerative disease.

Specifically, Applicants have shown that GAD_{65} gene transfer into glutamatergic excitatory neurons leads to an inhibitory bias with altered network activity. This phenotypic shift provides strong neuroprotection and demonstrates there is plasticity between excitatory and inhibitory neurotransmission in the mammalian brain that results in a therapeutic effect, in particular the alleviation of symptoms of Parkinson's disease. (Kaplitt Decl. para. 5-6.)

The same inventive concept of delivering GAD to a region of the central nervous system can be applied to any CNS disease in which increasing GABA production is desirable. (Kaplitt Decl. para. 7.) Applicants themselves **have used the method of the invention to reduce the symptoms of epilepsy by delivering GAD_{65} to a region of the brain involved in epilepsy**, e.g., the hippocampus. (Kaplitt Decl. para. 8-10; see also '746 Publication, para. [348] – [388] (Example 9).) Applicants delivered an AAV-GAD_{65} construct stereotaxically to a region of the brain (the hippocampus) that was at the time of the invention well known to be associated with epilepsy and ameliorated the symptoms of the disease.

Other groups have used the vectors and/or methods of the application to target regions of the brain to address other conditions such as metabolic disorders (Kaplitt Decl. para. 11-12) and chronic pain (Kaplitt Decl. para 13-14). This alone proves that the method of the invention could be used to deliver GAD_{65} to the brain of a subject having a neurodegenerative disorder other than Parkinson's Disease to ameliorate the symptoms of said disease.

Furthermore, the teachings of the application are not limited to the delivery methods of the examples. Other vectors, for example, may be used to target the CNS and alter GAD expression. (Kaplitt Decl. para. 13-14.)

Finally, it is obvious that GAD_{65} can be targeted specifically to different regions of the brain including the hippocampus (Kaplitt Decl. para. 8), the lateral nucleus of the hypothalamus (Kaplitt Decl. para. 12), the rostral agranular insular cortex (RAIC) (Kaplitt Decl. para. 14), and even the visual cortex (Kaplitt Decl. para. 16).

Thus, one of ordinary skill in the art would be able to use the application's disclosure, in addition to the knowledge available in the art, to apply the invention to alter expression of glutamic acid decarboxylase generally and GAD_{65} specifically in a selected region of the CNS. In summary, the disclosure in the application, in combination with the knowledge available in the art, would enable one skilled in the art to perform the full scope of the claimed invention without undue experimentation.

CONCLUSION

Applicants believe that all pending claims are allowable for the reasons stated above. Applicants invite the Examiner to call the undersigned attorney if there are any further questions and to speed prosecution.

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Respectfully submitted,

By_____

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